

USSN: 09/600,564
Response to Office Action of June 9, 2006
Atty. Docket: 100725-9 Kreisler1089
Page 7

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REMARKS

Claim Status

Claims 14-27 are in the case, claims 14-21 and 27 stand rejected; claims 22-26 are withdrawn, claims 14 and 27 have been amended.

Claim Rejections - 35 USC § 112, first paragraph

Claims 14-21 and 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement in that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

As stated by the examiner, the instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- synthesizing at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

This method requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration "sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major to his compatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible" and "... sufficiently short so that selection and proliferation accompanied by the specific elimination of particular T cells do not occur".

The examiner maintains his rejection, stating that the specification is silent with regard to

USSN: 09/600,564
Response to Office Action of June 9, 2006
Atty. Docket: 100725-9 Kreisler1089
Page 8

what incubation time for a given protein fragment and with regard to how one would determine if "particular T cells" have proliferated and elimination has occurred. Given that immunological (T cell) responses are antigen dependent, the examiner argues that one would not be able to predict what amount of time would be sufficient for the protein fragment or fragments to be sufficiently taken up by the major to his compatibility antigen (MHC) molecules where the taking up is sufficiently long when an unambiguous identification of stimulated T cells is possible and sufficiently short so that selection and proliferation accompanied by the specific elimination of particular T cells do not occur.

The examiner concludes by stating that the specification provides no working examples that provide guidance in making such a prediction. Consequently, since the amount of experimentation required to determine if a given protein or protein fragment would the protein fragment or fragments are sufficiently taken up by the major to his compatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible and sufficiently short so that selection and proliferation accompanied by the specific elimination of particular T cells do not occur would be undue, the specification is not enabling for the claimed method.

Applicant respectfully disagrees.

Applicant acknowledges with thanks the telephone discussion between the undersigned and Examiner Zeman. In the interview, three issues were discussed:

1. the time frame and guidance given from beginning to evaluation of results
2. the new matter rejection of claim 14, and
3. the new matter rejection of claim 16.

The 6 hour period present in the text was discussed as being a guide to the experimenter but the examiner stated his belief that the phrase "can be 6 hours" implied that other times might be appropriate. Applicant does not disagree but suggests that the issue is not whether other times may be appropriate. Rather, the issue is does the text provide sufficient guidance to allow one skilled in the pertinent art to determine such other times.

USSN: 09/600,564
Response to Office Action of June 9, 2006
Atty. Docket: 100725-9 Kreisler1089
Page 9

As to the second issue the examiner tentatively agreed that applicant could obviate his rejection of claim 14 by amending claim 14 from "proliferation accompanied by the elimination of T cells do not occur" to read "proliferation accompanied by the elimination of stimulated T cells do not occur." Applicant has done so by so amending claim 14.

With regard to claim 27, the examiner is concerned about the meaning of "specific elimination of particular T cells." The examiner is willing to acknowledge that the phrase relates to stimulated T cells, but is concerned that because of the heterogeneous grouping of T cells present, the phrase may mean a specific subset of the stimulated T cells rather than the complete set of stimulated T cells. Applicant suggests that the examiner's interpretation stretches the plain meaning of the term "specific" which in context means that the T-cells eliminated are specifically those that are stimulated and not those that are not.

In their response to the prior office action, applicants argued that anyone skilled in the art, i.e. in the setting up cell culture experiments, is aware that proliferation typically occurs not before 24 hours of stimulating T-cells and cited a standard immunology textbook, *Abbas, Abdul K., Cellular and Molecular Immunology*, Saunders Company, 1997, ISBN 0-7216-4024-9 (copy attached to earlier response) at page 160, Figure 7 – 9. Applicant also cited *Wells et al.* 1997, *The Journal of Clinical Investigation*, 100(12); 3173-3183 (copy attached to earlier response).

Applicant now submits with this response the declarations of Dr. Michael Raymond Betts of the University of Pennsylvania and Dr. Kirk Busch of the Technical University Munich. [see attached] Drs. Betts and Busch both declare that based on their own expertise in the field, the technique or process disclosed in the specification and claimed in the claims of the instant specification is known and has been used in many research labs since 1998. The two Declarations state that loading of peptides onto MHC molecules onto MHC Class I molecules occurs within the first 30 minutes of incubation.

In paragraph 8 the Declarations state that production of cytokines produced by

USSN: 09/600,564
Response to Office Action of June 9, 2006
Atty. Docket: 100725-9 Kreisler1089
Page 10

stimulated T-cells can be found at 6 hours and that maximum secretion occurs at approximately 12 hours after stimulation. Drs. Betts and Busch also declare that cell division will not occur within 24 hours after stimulation.

Of particular significance is paragraph 12 of the Declarations where the declarants state that the specification provides sufficient guidance to anyone skilled in the art to perform the claimed method and that setting up the assay with a 6 hour incubation time and then modifying the time will allow everybody to use the method and determine the optimum incubation period.

A time sufficiently short to avoid proliferation would therefore be understood as a time of approximately 24 hours after stimulation. [Declarations, para. 10]

A time sufficiently long to allow production of cytokines is approximately 6 hours after stimulation. [Declarations, para. 8]

Thus, applicant believes that one skilled in the art is readily able to utilize the present disclosure in conjunction with the existing art to determine the appropriate time frame.

Claim Rejections - 35 USC § 112, second paragraph

Claim 27 stands rejected under 35 USC § 112, second paragraph as being indefinite for the use of the phrase in that the phrase "selection and proliferation accompanied by the specific elimination of particular T cells do not occur."

Applicant has amended claim 27 to substitute "stimulated" for "particular" and believes this obviates that basis for the rejection.

Claim Rejections - 35 USC § 112, first paragraph

Claims 14-21 and 27 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in sufficient detail to convey to one skilled in the relevant art that applicant had possession of the claimed invention in that the phrase "proliferation accompanied by the elimination of T cells do not occur." is new matter.

USSN: 09/600,564
Response to Office Action of June 9, 2006
Atty. Docket: 100725-9 Kreisler1089
Page 11

Applicant traverses this ground for rejection with regard to claims 14-21 and 27.

Applicant apologizes to the examiner for not specifically referencing, in the last response, that portion of applicant's specification that provides support for the phase. Such support appears at page 5, second paragraph, of the specification.

As support is present, applicant respectfully requests that this rejection be withdrawn.

Claim 16 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in sufficient detail to convey to one skilled in the relevant art that applicant had possession of the claimed invention in that the phrase "the suspension comprises cells which present the protein fragment bound to MHC class I or class II molecules." This is a new matter rejection.

Applicant traverses this ground for rejection.

Applicant apologizes to the examiner for not specifically referencing, in the last response, that portion of applicant's specification that provides support for the phase. Such support appears at page 7, second paragraph, of the specification.

As support is present, applicant respectfully requests that this rejection be withdrawn.

Conclusion

Applicant believes these remarks and the claim amendments are sufficient to obviate the grounds for rejection presented in the outstanding office action and respectfully requests allowance of the pending claims. Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,
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